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Gina N. Shishima
FULBRIGHT & JAWORSKI L.L.P.
SUITE 2400
600 CONGRESS AVENUE
AUSTIN, TX 78701

EXAMINER	
AEDER, SEAN E	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,559	DAWSON ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/14/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8-12,15-25,27,32-39 and 42-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 6, 8-12, 15-25, 27, 32-39, and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413). Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 8/14/06 in response to the Office Action of 4/10/06 are acknowledged and have been entered.

Claims 1-6, 8-12, 15-25, 27, 32-39, and 42-46 were pending.

Claims 1, 3, 5, 8, 12, 22, 25, 39, and 44 have been amended by Applicant.

Claim 4 has been cancelled by Applicant.

Claims 1-3, 5, 6, 8-12, 15-25, 27, 32-39, and 42-46 are currently under examination.

The text of those sections of Title 35 U.S.C. code not included in this Office Action can be found in a prior Office Action.

The following Office Action contains NEW GROUNDS of rejections.

Objections Withdrawn

The objections to the specification are withdrawn in view of amendments.

The objection to the drawings is withdrawn in view of the newly submitted drawings.

The objection to claim 39 is withdrawn in view of amendments.

Rejections Withdrawn

The rejection of claims 22, 23, 44, and 45 under 35 U.S.C., second paragraph, is withdrawn in view of amendments.

Response to Arguments

35 USC § 112, first paragraph, Written Description Rejection

The rejection of claims 1-3, 5, 6, 8-11, 15-21, 24, 27, 32-38, 42, 43, and 46 under 35 U.S.C., first paragraph, for failing to comply with the written description requirement, is maintained for the reasons stated in the Office Action of 4/10/06 and for the reasons set-forth below.

The Office Action of 4/10/06 contains the following text:

"The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of "PPT1 modulators". However, the written description in this case only sets forth the PPT1 modulator DAP1, peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12), and Didemnin B. The specification does not disclose any other PPT1 modulators, including other peptides or peptide mimetics of any other sequences, as broadly encompassed in the claims.

The specification teaches PPT1 modulators include any molecule that selectively, competitively, or specifically interacts with PPT1 and specifically inhibits or

enhances its activity. Further, the specification discloses that PPT1 modulators may be a protein or a peptide, a small molecule, or a nucleic acid molecule (page 6 lines 14-18, in particular). However, the written description only reasonably conveys the PPT1 modulator DAP1 (pages 152-153 and pages 158-159, in particular) peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12) (claim 25, in particular), and Didemnin B (page 4, in particular). A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural features that are common to the genus. That is, the specification provides neither a representative number of species that encompass the genus of PPT1 modulators nor does it provide a description of structural features that are common to PPT1 modulators. Further, the specification does not provide a written description of any other specific peptide mimetic that

modulates PPT1 other than a peptide mimetic of VKIKK (SEQ ID NO:12). Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of DAP1, peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12), and Didemnin B is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of PPT1 modulators, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only PPT1 modulators wherein said PPT1 modulators are DAP1, peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12), or Didemnin B, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115)."

In response to the Office Action of 4/10/06, Applicant argues that Examiner's reliance on Regents of the University of California v. Eli Lilly and Co., 119 F. 3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (Fed. Cir. 2004) appears to be misplaced regarding the written description requirement. The Response states that in Lilly, the specification was drawn to rat insulin cDNA, yet the claims were drawn to human insulin cDNA. Further, the specification did not provide adequate written description of human insulin cDNA, as only a prophetic example was provided in which human insulin cDNA was described without any distinguishing information concerning its identity. The Response further states that in Rochester, the written description for the claims was not satisfied since the claims were drawn to a method of enzyme inhibition by administration of a non-steroidal compound, but no such compounds were described in the specification. Regarding Lilly, Applicant states that the present claims regard the same species as described in the specification – specifically, PPT1 modulators that competitively inhibit PPT1.

Applicant further states that the specification describes numerous examples and enabling descriptions of subject matter of the rejected claims. Applicant further states that examples in the specification set apart the present case from Rochester since the present specification allegedly provides numerous examples of PPT1 modulators of the claimed invention. Applicant states that these examples include peptide mimetic VKIKK, nucleic acid molecules, polypeptides, proteins, peptides, small molecules, antibodies, peptide mimetics, PPT1 modulators attached to lipid components, chemically modified PPT1 modulators, amino acid variants, and peptides corresponding to one or more antigenic determinants of the PPT1 polypeptide. Applicant further cites the following passage from the Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, first paragraph: "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus". Applicant states: "Addressing the functional aspect....claim 1...has been amended to recite the following: "A method of inhibiting a cancer cell comprising administration to the cancer cell a composition comprising a PPT1 modulator in an amount effective to reduce PPT1 activity level, wherein the modulator competitively binds to PPT1"". Applicant further concludes that the specification provides a sufficient physical description of the

functional aspects of PPT1 modulators as set forth in independent claim 1, in that they must be competitive inhibitors of PPT1. Applicant further states that the specification provides examples of how one would make and use peptide mimetic VKIKK, nucleic acid molecules, polypeptides, proteins, peptides, small molecules, antibodies, peptide mimetics, PPT1 modulators attached to lipid components, chemically modified PPT1 modulators, amino acid variants, and peptides corresponding to one or more antigenic determinants of the PPT1 polypeptide.

The amendments to the claims and the arguments found in the Response filed 8/14/06 have been carefully considered, but are not deemed persuasive. In regards to the argument that the species of the pending claims are described in the specification, the Examiner would like to point-out that "PPT1 modulators that competitively inhibit PPT1" is a genus. The only Examples of said genus that are provided with an enabling disclosure are: the PPT1 modulator DAP1 (pages 152-153 and pages 158-159, in particular) peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12) (claim 25, in particular), and Didemnin B (page 4, in particular). Further, it is noted that Rochester was cited in the Office Action of 4/10/06 in order to point-out that the decisions of Lilly were applicable to products other than cDNAs. Further, a prophetic list of uncharacterized, and structurally undescribed products (nucleic acid molecules, polypeptides, proteins, peptides, small molecules, antibodies, peptide mimetics, PPT1 modulators attached to lipid components, chemically modified PPT1 modulators, amino acid variants, and peptides corresponding to one or more antigenic determinants of the PPT1 polypeptide), does not provide a written description of the claimed invention. As

conceded in the Reply of 8/14/06, the Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, first paragraph, states: "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus". The specification lacks (1) sufficient description of a representative number of species by reduction to practice, (2) sufficient description of a representative number of species by reduction to drawings, (3) sufficient description of a representative number of species by disclosure of functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical

name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id. Although the inventions at issue in Lilly were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Applicability to the claims such as those here is supported by University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004), where the court has

since clarified that this standard applies to compounds other than cDNAs. In this instant case, a disclosure that the claimed product includes nucleic acid molecules, polypeptides, proteins, peptides, small molecules, antibodies, peptide mimetics, PPT1 modulators attached to lipid components, chemically modified PPT1 modulators, amino acid variants, and peptides corresponding to one or more antigenic determinants of the PPT1 polypeptide, does not provide information concerning which structural features are present in the claimed genus. Further, said disclosure provides no correlation between specific structure and function. For instance, the specification does not describe which polypeptide sequences would or would not function as a PPT1 modulator. Further, the specification does not describe which structural features of small molecules would enable said small molecule to function as a PPT1 modulator.

Further, *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of PPT1 modulators, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The

compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only PPT1 modulators wherein said PPT1 modulators are DAP1, peptide mimetics of the amino acid sequence VKIKK (SEQ ID NO:12), or Didemnin B, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115)." However, it is noted that a disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

35 USC § 112, first paragraph, Enablement Rejection

The rejection of claims 1-3, 5, 6, 8-12, 15-25, 27, 32-39, and 42-46 under 35 U.S.C., first paragraph, for failing to comply with the enablement requirement, is maintained for the reasons stated in the Office Action of 4/10/06 and for the reasons set-forth below.

The Office Action of 4/10/06 contains the following text:

"The claims are broadly drawn to a method of inhibiting *any* activity of *any* type of cancer cell in vitro *and in an animal* comprising administering to the cancer cell *any* PPT1 modulator.

The specification discloses a method of *inhibiting cell survival and inhibiting cell proliferation* in several cancer cell lines grown *in vitro* comprising administering to said cells the PPT1 modulator DAP1 (pages 152-154 and pages 157-159, in particular). Further, the prior art discloses a method of inhibiting cell proliferation in a leukemia cell line grown in vitro comprising administering the PPT1 modulator Didemnin B (see Rinehart et al (Science, 1981, 22(4497): 933-935) as evidenced by Meng et al (Biochemisty, 1998, (37): 10488-10492)). However, the specification does not provide any working examples demonstrating that DAP1 inhibits any activity other than cell survival and cell proliferation. Further, the specification does not provide any working examples demonstrating that Didemnin B inhibits any activity other than cell proliferation. Further, the specification provides prophetic guidance for administering DAP1 to an animal (Example 4); however, the specification does not provide any working examples that would indicate DAP1 or Didemnin B would predictably inhibit *any* activity of a cancer cell *in an animal*. Further, the specification provides no indication that any PPT1 modulator of the elected group other than DAP1 or Didemnin B that would predictably inhibit an activity of a cancer cell grown in vitro or found in an animal.

Although Applicant is enabled for a method of inhibiting certain properties of cancer cells grown in vitro by treating said cells with DAP1 or Didemnin B, Applicant is not enabled for a method of inhibiting any activity of any type of cancer cell found in an

animal comprising administering any PPT1 modulator of the elected group. Those of skill in the art recognize that in vitro assays and cell culture based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assay does not permit a single extrapolation of an in vitro assay to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well know in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p.4, see Major Difference In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "Petri dish cancer" is a poor representation of malignancy, with characteristics

profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well know in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, 1997, 278:1041-1042.) who discusses the potential shortcoming of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with cologenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041 first column, in particular) wherein the fundamental problem in drug discovery for cancer is that the model systems are **not predictive**. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above and the lack of guidance, workable examples and/or exemplification in the specification, it would require undue experimentation by

one of skill in the art to determine with any predictability, that the method would function as claimed. Thus, while the specification is enabling for a method of *inhibiting cell survival* and *inhibiting cell proliferation* of *cultured cancer cell lines grown in vitro* by administering *DAP1 or Didemnin B*, the specification lacks reasonable guidance, predictability, and objective evidence that enables a method of inhibiting any activity other than cell survival and cell proliferation of cancer cells cultured in vitro. Further, the specification lacks reasonable guidance, predictability, and objective evidence that the method would function as claimed in an animal or that the method would function as claimed in vitro using any PPT1 modulator of the elected invention other than DAP1 or Didemnin B."

In response to the Office Action of 4/10/06, Applicant states that the specification is enabling for methods of inhibiting a cancer cell, such as altering proliferation, metastasis, contact inhibition, soft agar growth, cell cycle regulation, tumor formation, tumor progression, differentiation, programmed cell death, or tumor invasion using any modulator of PPT1, wherein said modulator is a competitive inhibitor of PPT1. Applicants state that compliance with the requirements for enablement under 35 U.S.C., first paragraph, does not require that an example is disclosed or that the invention be reduced to practice prior to filing. Further, Applicant points-out that the PTO is required to assume that the specification complies with the enablement requirement unless it has "acceptable evidence or reasoning" to suggest otherwise. Applicant states that Examiner failed to provide a factual basis or scientific principal to reasonably doubt the accuracy of the present disclosure. Applicant states that Examiner has offered no

evidence that the PPT1 modulators of the present invention would not inhibit a cancer cell as claimed. Applicant further provided a copy of a Rapid Access to NCI Discovery Resources report dated 1/23/06, which indicates doses of 25 mg/kg of DAP1-amide were tolerated when administered to nude mice via i.v. injection and gave a serum concentration of 70μM after 2hrs. Applicant further states that this level was effective in killing the tumor cells in an in vitro assay. Applicant further states that human glioblastoma cells were then grown in mice, wherein intraperitoneal administration at 100 mg/Kb/day resulted in no observed toxicity and plasma levels of 100-200mM were shown four hours post-dosing. Applicant further stats that this study supports the use of the compounds in vivo since previous in vitro time-course studies indicated that continuous drug levels of 50-100 μM were necessary to inhibit cell growth.

The amendments to the claims and the arguments found in the Response of 8/14/06 have been carefully considered, but are not deemed persuasive. As stated in the Office Action of 4/10/06, although Applicant is enabled for a method of inhibiting certain properties of cancer cell grown in vitro by treating said cells with DAP1 or Didemnin B, Applicant is not enabled for a method of inhibiting any activity of any type of cancer cell found in an animal comprising administering any PPT1 modulator of the elected group. Those of skill in the art recognize that in vitro assays and cell culture based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, in vivo correlations are generally lacking for the reasons described in the Office Action of 4/10/06. Further, no other type of cancer cell inhibition (in vivo or in vitro), such as

altering metastasis, contact inhibition, soft agar growth, tumor formation, tumor progression, differentiation, programmed cell death, or tumor invasion using any modulator of PPT1, wherein said modulator is a competitive inhibitor of PPT1, is supported by the disclosure or the art.

Treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, 1997, 278:1041-1042.) who discusses the potential shortcoming of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with cologenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041 first column, in particular) wherein the fundamental problem in drug discovery for cancer is that the model systems are **not predictive**. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

Further, it is noted that the teachings of Rapid Access to NCI Discovery Resources report dated 1/23/06 merely indicate that DAP1-amide can be "tolerated" in vivo and that levels of DAP1-amide that are said to inhibit growth of tumor cells in vitro are achieve in the serum of mice injected with DAP1-amide. The teachings of Rapid Access to NCI Discovery Resources report dated 1/23/06 do not demonstrate that any or all PPT1 modulators would alter metastasis, tumor formation, tumor progression, differentiation, or programmed cell death of cancer cells in vivo. Taking into account the

teachings of Freshney, Derma, and Gura (see above), the teachings of Rapid Access to NCI Discovery Resources report dated 1/23/06 provide no indication that DAP1-amide would inhibit a cancer cell in vivo. Therefore, the teachings of Freshney, Derma, and Gura provide acceptable evidence or reasoning that the claimed invention is not enabled.

In view of the teachings above and the lack of guidance, workable examples and/or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed. Thus, while the specification is enabling for a method of *inhibiting cell survival* and *inhibiting cell proliferation* of *cultured cancer cell lines grown in vitro* by administering *DAP1 or Didemnin B*, the specification lacks reasonable guidance, predictability, and objective evidence that enables a method of inhibiting any activity other than cell survival and cell proliferation of cancer cells cultured in vitro. Further, the specification lacks reasonable guidance, predictability, and objective evidence that the method would function as claimed in an animal or that the method would function as claimed in vitro using any PPT1 modulator of the elected invention other than DAP1 or Didemnin B.

35 USC § 102(b)

The rejection of claims 1-3, 5, 8, 9 rejected under 35 U.S.C. 102(b) as being anticipated by Rinehart et al (Science, 1981, 22(4497): 933-935) as evidenced by Meng

et al (Biochemisty, 1998, (37): 10488-10492) is maintained for the reasons found in the Office Action of 4/10/06 and for the reasons set-forth below.

The Office Action of 4/10/06 contains the following text:

"The claims are drawn to a method of inhibiting the proliferation of a cancer cell comprising administering to said cell a composition comprising a proteinaceuous PPT1 modulator that selectively interacts with and inhibits the activity of PPT1.

Rinehart et al teaches a method of inhibiting leukemia cell proliferation comprising administering Didemnin B (see page 212 last paragraph, in particular). Further, Rinehart et al teaches Didemnin B is a proteinaceous compound (see Figure 1, in particular). Further, as evidenced by Meng et al, Didemnin B functions as an agonist that selectively interacts with and inhibits the activity of PPT1 (see abstract of Meng et al, in particular)."

In the Response dated 8/14/06, Applicant amended claim 1 to recite: "A method of inhibiting a cancer cell comprising administering to the cancer cell a composition comprising a PPT1 modulator in an amount effective to reduce PPT1 activity level, wherein the modulator competitively binds to PPT1". Applicant states that Meng et al teaches that Didemnin B noncompetitively inhibits PPT1. Applicant further argues that claim 1 recites modulators of PPT1 that are competitive inhibitors of PPT1. Applicant then concludes that Meng et al does not teach each and every element of the claimed invention.

The amendments to the claims and the arguments found in the Response of 8/14/06 have been carefully considered, but are not deemed persuasive. The claims

are drawn to a method of inhibiting a cancer cell comprising administering to the cancer cell a composition comprising a PPT1 modulator in an amount effective to reduce PPT1 activity level, wherein the modulator competitively binds to PPT1. Meng et al teaches a method of inhibiting leukemia cell proliferation comprising administering Didemnin B (see page 212 last paragraph, in particular). Further, Rinehart et al teaches Didemnin B is a proteinaceuous compound (see Figure 1, in particular). Further, as evidenced by Meng et al, Didemnin B functions as an agonist that selectively interacts with and inhibits the activity of PPT1 (see abstract of Meng et al, in particular). It is noted that the claims are not drawn to a method using a modulator that "competitively inhibits" PPT1; rather, the claims are drawn to a method using a modulator that "competitively binds" PPT1. Since the modulator taught by Meng selectively interacts with PPT1 (see abstract of Meng et al, in particular), one of skill in the art would recognize that said modulator would competitively inhibit binding of other agents that bind to PPT1.

New Rejections Based on Amendments

Claims 1-3, 5, 6, 8-12, 15-25, 27, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependent claims 2, 3, 5, 6, 8-12, 15-25, 27, and 33 are rejected as indefinite for reciting: "...wherein the modulator competitively binds to PPT1". It is not clear from the claims or the specification what is meant by "competitively binds to PPT1". This renders the claim indefinite because the term "competitively binds to

PPT1" is not defined by the claim and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, claim 1 is indefinite for not indicating with what said modulator is competing. Given the above reasons, the metes and bounds of the claims cannot be determined.

Summary

No claim is allowed. Claims 6, 10-12, 15-25, 27, 32-39, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, but free of the prior art teaching a method of inhibiting a cancer cell comprising administering to the cancer cell a composition comprising a PPT1 modulator in an amount effective to reduce PPT1 activity level, wherein the modulator competitively binds to PPT1, wherein the modulator decreases the amount of PPT1 or is a peptide mimetic that interacts with PPT1. The closest prior art for claims 6, 10-12, 15-25, 27, 32-39, and 42-46 is Rinehart et al (Science, 1981, 22(4497): 933-935); however, this reference does not teach or suggest a method of inhibiting a cancer cell comprising administering to the cancer cell a composition comprising a PPT1 modulator in an amount effective to reduce PPT1 activity level, wherein the modulator competitively binds to PPT1, wherein the modulator decreases the amount of PPT1 or is a peptide mimetic that interacts with PPT1.

Conclusion

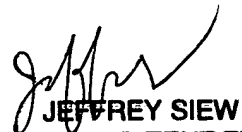
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a). A shortened statutory period for response to

this Final Action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this Final Action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. '1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than six months from the date of this Final Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

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